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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,383	05/18/2005	Alexander L. Klibanov	22078-2TARGESON	5031

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EXAMINER	
DIBRINO, MARIANNE NMN	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,383	KLIBANOV ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/14/04, 5/18/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *21-29,31,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20,30,32 and 33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10/14/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/16/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments filed 10/14/04 and 5/18/05 and Applicant's responses filed 7/15/08 and 11/5/07 are acknowledged and have been entered.

2. Applicant's election with traverse of Group I and species of membrane comprising a lipid, fluorine-containing gas, mean diameter of about 1 to 10 micrometers, membrane comprising an antibody and diagnostic composition useful for ultrasound imaging in responses filed 7/15/08 and 11/5/07, respectively, is acknowledged.

The basis of Applicant's traversal (of record in the response filed 11/5/07 on page 2) is that Applicant believes that the subject matters of Groups IV, VII, VIII and XI are capable of examination along with Group I without imposing a serious burden upon the Patent Office.

Applicant's arguments have been fully considered, but are not persuasive.

The standard for lack of unity is: that the Groups lack the same or corresponding special technical features. The Requirement mailed 10/4/07 meets this criterion at item #3 on page 3, i.e., and the issue of serious burden argued by Applicant is irrelevant.

However, not withstanding, serious burden may be shown by one or more of the following:

(a) the inventions have acquired a separate status in the art in view of their different classification;
(b) the inventions have acquired a separate status in the art due to their recognized divergent subject matter;
(c) the inventions require a different field of search (for example, searching different classes/subclasses or electronic resources, or employing different search queries);
(d) the prior art applicable to one invention would not likely be applicable to another invention;
(e) the inventions are likely to raise different non-prior art issues under 35 U.S.C. 101 and/or 35 U.S.C. 112, first paragraph.

In the instant case, Groups IV, VII, VIII and XI are methods of using the claimed product (Groups IV, VIII and XI) or making the claimed product.(Group VII). The method claims would be classified in different classes; for instance, Group IV would be classified in Class 435, subclass 484, Groups VIII and XI would be classified in Class 424 whereas elected Group I drawn to the product would be classified in Class 530, subclass 391.1. *In vivo* methods of treatment such as in Group XI, are likely to raise different non-prior art issues.

The requirement is still deemed proper and is therefore made FINAL.

However, upon reconsideration, the Examiner has rejoined Groups II and III to Group I.

Accordingly, claim 31 (non-elected species of Group I) and claims 21-29, 34 and 35 (non-elected groups IV-XIII) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 1-20, 30, 32 and 33 are presently being examined.

3. The use of the trademark SPECTRAMAX™ has been noted in this application, for example on page 24 at line 27. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware of in the specification.

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-15, 30, 32 and 33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

a. Claim 30 is indefinite in the recitation of "wherein the liquid carrier is a pharmaceutically acceptable liquid carrier" because it is not clear what is meant, *i.e,* the recitation is "A pharmaceutical composition, comprising a microbubble composition according to claim 1, wherein *the liquid carrier* [Examiner emphasis] is a pharmaceutically acceptable liquid carrier." No prior recitation of a liquid carrier is as being comprised in the pharmaceutical composition appears in the claim.

b. Claim 33 is indefinite in the recitation of "A pharmaceutical composition according to claim 32, which is an ultrasound contrast agent" because it is not clear what is meant, *i.e.*, a pharmaceutical composition comprising a microbubble may comprise an ultrasound contrast agent, but is not an ultrasound contrast agent.

c. Claim 1 is indefinite in the recitation of "substantially having crenated microbubble membranes" because it is not clear what is meant, *i.e.*, one of ordinary skill in the art would not know what is meant by substantially having crenated microbubble membranes," particularly in light of the disclosure of wrinkled, folded and non-spherical microbubble membranes in the instant specification and no disclosure of a distinction between them.

d. Claim 9 is indefinite in the recitation of "said microbubbles substantially having microbubble membranes having surface projections" because it is not clear what is meant, *i.e.*, what the metes and bounds of the claim are. Except for "fold" recited in dependent claim 10, one of ordinary skill in the art would not know what is meant by "substantially having...surface projections."

8. For the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of PCT/US03/21712, *i.e.*, 7/11/03, as the provisional parent application 60/395,179 does not support the claimed limitations of the instant application.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

10. Claims 16-20 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. 6,193,951 B1.

U.S. 6,193,951 B1 discloses microparticules or microbubbles comprising a membrane and containing a gas, liquid or solid for use as a contrast agent for ultrasonic contrast imaging. U.S. 6,193,951 B1 discloses that the microbubbles may be non-spherical, and about 1 micron to less than about ten microns in order to pass through the capillaries of the circulatory system. U.S. 6,193,951 B1 discloses that the membranes may be made from proteins or polymers and may be altered to include a targeting moiety such as antibodies or fragments thereof for binding to selected tissues such as to cell surface receptors. U.S. 6,193,951 B1 discloses use of a blood insoluble gas within the microbubbles.

It is an inherent property that non-spherical microbubble membranes exhibit increased deformability under shear relative to corresponding spherical microbubble membranes.

11. Claims 16-20 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. 6,193,951 B1.

U.S. 6,193,951 B1 discloses microparticules or microbubbles comprising a membrane and containing a gas, liquid or solid for use as a contrast agent for ultrasonic contrast imaging. U.S. 6,193,951 B1 discloses that the microbubbles may be non-spherical, and about 1 micron to less than about ten microns in order to pass through the capillaries of the circulatory system. U.S. 6,193,951 B1 discloses that the membranes may be made from proteins or polymers and may be altered to include a targeting moiety such as antibodies or fragments thereof for binding to selected tissues such as to cell surface receptors. U.S. 6,193,951 B1 discloses use of a blood insoluble gas within the microbubbles.

It is an inherent property that non-spherical microbubble membranes exhibit increased deformability under shear relative to corresponding spherical microbubble membranes.

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

13. Claims 1-20, 30, 32 and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. 6,372,195 B1 (IDS reference) in view of U.S. 6,548,048 B1 (IDS reference) as evidenced by an admission in the instant specification on page 16 at lines 14-27 and page 17 at lines 1-8.

U.S. 6,372,195 B1 discloses microbubbles that are made in a container by loading two gases, one of which is leached out after the microbubbles are formed, reducing the volume of the microbubbles each by about 75%. U.S. 6,372,195 B1 further discloses that the microbubble membranes are made of one or more surfactants such as carbohydrates, fatty acid esters of sugars, proteins or proteinaceous materials, or polysaccharides. U.S. 6,372,195 B1 discloses that the gas that is loaded and remains after volume reduction (*i.e.,* the gas osmotic agent) may be fluorine-containing gas, and the size of the microbubbles is not more than about 5 to 10 *um* (*i.e.*, micrometers). U.S. 6,372,195 B1 also discloses that the gas osmotic agent preferably has limited solubility in blood. U.S. 6,372,195 B1 discloses use of compositions comprising microbubbles as ultrasound contrast agents suspended in a pharmaceutically acceptable liquid carrier (especially abstract, column 2 at lines 58-63, column 3 at lines 13-31 and lines 52-67, column 4 at lines 1-15 and lines 32-44, column 5 at lines 33-50, column 6 at lines 24-33, column 35-56, column 13 at lines 63-67, column 14 at lines 1-4 and lines 14-27, Table 1, and claims).

U.S. 6,372,195 B1 does not disclose wherein the microbubble membranes include binding targeting molecules that bind to the target, including wherein the molecules are antibodies.

U.S. 6,548,048 B1 discloses gas-filled, including fluorine-gas containing, microbubble compositions, which membranes are lipopeptides) for use as ultrasound contrast agents, said microbubbles having targeting molecules that are antibodies that have affinity for a particular target site or cells, said microbubbles being no larger than about 10 microns. U.S. 6,548,048 B1 discloses that some of the other targeting vectors may be peptides or proteins that bind to receptors, oligonucleotides, or small molecules (entire reference, especially abstract, column 5 at lines 25-67, column 6 at lines 1-67, column 7 at lines 1-37, claims).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have included a targeting antibody such as disclosed for the targeted microbubble of U.S. 6,548,048 B1 in the microbubble disclosed by U.S. 6,372,195 B1.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a targeted ultrasound contrast agent composition.

With regard to the limitation "wherein the gas is substantially insoluble in blood" recited in instant claims 3, 12 and 18, the primary art reference discloses that the gas should have limited solubility in blood, and it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a gas that is substantially insoluble in blood so that the gas would be maintained within the microbubble when it is administered *in vivo*, maintaining ultrasound contrast enhancement.

With regard to the limitation "said microbubbles substantially having crenated microbubble membranes" recited in instant base claim 1, "said microbubbles substantially having microbubble membranes having surface projections" recited in instant base claim 9 and "said microbubbles predominantly having non-spherical microbubble membranes" recited in instant base claim 16, while the reference does not explicitly disclose that the microbubble membranes are crenated, are non-spherical, or have surface projections such as folds, it does disclose a 25% reduction in volume after loss of the first gas comprised in said microbubble.

The admission in the instant specification on page 16 at lines 14-31 and page 17 at lines 1-8 is that a spherical microbubble can be modified by reducing the volume of entrapped gas, wherein the excess membrane material will typically form protrusions from the microbubble membrane, which can be described as crenations, folds, wrinkles or other irregualities, and that at least about 10% of the gas is removed to convert spherical microbubbles to non-spherical microbubbles, but the amount may be higher.

Therefore the claimed microbubble composition appears to be the same or similar to the microbubble composition of the prior art absent a showing of unobvious differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the microbubble composition of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

14. No claim is allowed.
15. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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September 9, 2008

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